# Is Microscopic Colitis a Drug-induced Disease?

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**Abstract:** Microscopic colitis (MC) is diagnosed in up to 13% of patients investigated for chronic diarrhea, particularly in middle-aged and elderly patients. Recent studies have suggested an etiological role for various drugs, including nonsteroidal anti-inflammatory drugs and proton pump inhibitors. To ascertain the potential role for drug exposure in the development of MC, we performed a systematic review based on a MEDLINE search and conducted a meta-analyses on the available data. We also give an overview of the case reports and studies illustrating the role of drugs in inducing MC. A number of hypotheses are formulated with regard to the potential pathophysiological mechanisms in drug-induced MC. However, confirmative evidence is still largely lacking. Considering the high number of drug users and the relatively low incidence of MC, it is more likely that drug-induced cases of MC are the result of an idiosyncratic reaction.

**Key Words:** microscopic colitis, drug exposure, proton pump inhibitors, NSAIDs, systematic review, collagenous colitis, lymphocytic colitis

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Microscopic colitis (MC) is an umbrella term for collagenous colitis (CC) and lymphocytic colitis (LC). MC is characterized by the combined presence of watery diarrhea, a macroscopically normal ileocolonoscopy and typical microscopic findings.[1] The histologic changes of MC comprise an increased number of intraepithelial $CD8^+$ T lymphocytes, exceeding 20 per 100 surface epithelial cells, accompanied by superficial epithelial damage and a variable inflammatory infiltrate in the lamina propria. In addition, in CC, a thickened subepithelial collagen band, which exceeds 10 μm, is present. These histologic characteristics are not pathognomic as they may occur in various inflammatory conditions in the colon.[2]

MC can be diagnosed in patients of any age, but primarily affects the elderly. The average age of patients diagnosed with LC or CC ranges from 53 to 69 years.[3] Also, MC seems to be more frequent in women than in men. In the past, MC was thought to be a rare disorder. However, it has recently become apparent that MC is diagnosed in up to 13% of patients investigated for chronic diarrhea, particularly if middle-aged or elderly.[2,4] Pardi et al[4] reported an increasing annual incidence rate up to 7.1 for CC and up to 12.6 for LC per 100,000 person-years in the period of 1998 to 2001. Along the same line, Scandinavian studies have also shown increasing incidences for both LC and CC (Table 1).

It is apparent that the induction of inflammation in the lamina propria is a key pathogenetic factor in MC. However, the exact mechanisms involved in the initiation and development of MC remain to be elucidated and several pathophysiological mechanisms have been proposed. Genetic susceptibility was suggested because of reports of familial clustering of the disease.[10,11] Secondly, the reported seasonal variation in incidence indicates an infectious cause.[12] To date, no causal enteropathogen has been identified and antibiotics are not effective in the treatment of MC. Over 40% of the patients with MC have coexisting autoimmune diseases such as celiac disease or thyroiditis pointing to potential involvement of autoimmune mechanisms.[2,6,13] Furthermore, for CC, myofibroblast dysfunction has been described.[14–16] Finally, noxious luminal substances such as drugs and smoking may trigger the chronic inflammation seen in MC and one postulated hypothesis points to increased colonic permeability in MC patients, thereby allowing luminal antigens to enter the lamina propria and elicit an immune and inflammatory reaction.[17]

The increasing incidence of MC may partially be explained by an increased awareness of the condition among clinicians and histopathologists. Moreover, a variety of drugs has been associated with MC and has even been suggested to induce MC. The increased use of medications especially in older people might explain the reported increased incidence of MC.[3] To shed more light with regard to current evidence regarding the role of drug exposure in MC and the mechanisms involved we performed a systematic review of the literature.

## MATERIALS AND METHODS

### Literature Search

We executed a MEDLINE search using the terms: "microscopic colitis" or "lymphocytic colitis" or "collagenous colitis." The language restrictions were English, French,

**TABLE 1.** Incidence Rates (per 100,0000) of Collagenous Colitis (CC) and Lymphocytic Colitis (LC)

| | Period Investigated | CC | LC | References |
|---|---|---|---|---|
| USA | 1985-1997 | 1.6 | 2.7 | Pardi et al[4] |
| | 1998-2001 | 7.1 | 12.6 | |
| Sweden | 1984-1993 | 1.8 | No data | Bohr et al[5] |
| | 1993-1998 | 4.9 | 4.4 | Olesen et al[6] |
| Iceland | 1995-1998 | 5.2 | 4.0 | Agnarsdottir et al[7] |
| Spain | 1993-1997 | 2.3 | 3.7 | Fernandez-Banares et al[8] |
| Canada | 2002-2004 | 4.6 | 5.4 | Williams et al[9] |

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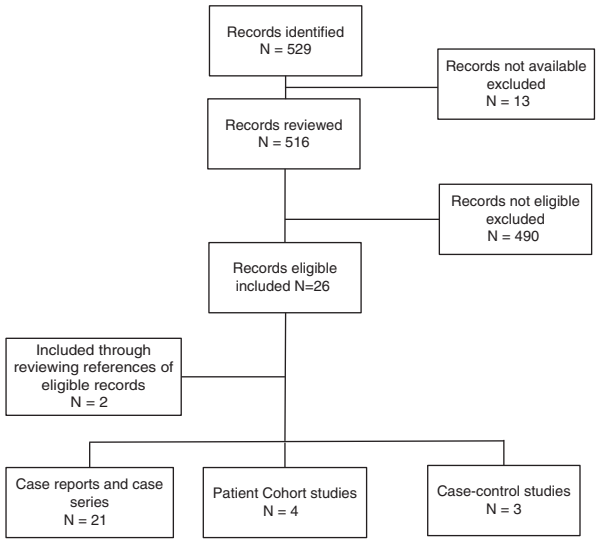


**FIGURE 1.** PRISMA flowchart for literature search.

German, or Dutch. The initial search resulted in 529 hits. The abstract, or when available, the full paper was reviewed by 2 reviewers independently and papers were excluded if not reporting on drugs and MC. For 13 hits, no abstract or paper was available and were therefore excluded. After initial review, 26 papers were found eligible for further review. Review of the references of the included papers resulted in 2 additional case reports (see Fig. 1 for PRISMA flowchart).

## Meta-analysis

Eventually, the meta-analysis was performed using data from the only 3 case-control studies assessing exposure to medication in MC.[18–20] These 3 studies all reported on nonsteroidal anti-inflammatory drugs (NSAIDs) and only 2 of them on proton pump inhibitors (PPIs). Therefore, only data on NSAID exposure were considered for meta-analysis. Also, the patient populations examined were not entirely homogenous, some examining CC and LC separately, for instance. For this reason, in case of the study of Fernandez-Banares et al,[19] we pooled the drug exposure rates from CC and LC cases before the meta-analysis.

For each of the included studies, odds ratios (ORs) and their 95% confidence intervals were calculated based upon the reported drug exposure rates in MC patients and controls. To derive a pooled OR from individual studies, we used a random-effects meta-analysis model. It is important to note, that we were not able to correct ORs for age, sex, and other confounders and therefore only report crude ORs. Heterogeneity was quantified with the $I^2$ index, which describes the proportion of total variation in study estimates due to heterogeneity.[21]

Statistical analyses were conducted using the "metan" command within Stata version 11 (Stata Corp., College Station, TX). The results are displayed in a forest plot.

# RESULTS AND DISCUSSION

## NSAIDs

Of all drug groups suggested to play an etiological role in MC, the most convincing evidence exists for NSAIDs. A summary of case reports of NSAID-induced MC is given in Table 2. We also present a summary of cases reporting on the association with the exposure to Cyclo 3 forte, a venotonic drug used in France, also containing aspirin (Table 3). It is, however, important to acknowledge that it is unclear whether the association is related to aspirin or the other components on Cyclo 3 forte.

In an early prospective study, NSAIDs were implicated in 10% of newly diagnosed cases of colonic inflammation, and patients taking NSAIDs had a 5-fold risk for developing a colonic disease.[29] In later years, a substantial number of studies have reported on a positive association with NSAID exposure and MC[20,23,30–32] (see Table 4 for cohort studies). This association seems more apparent with CC.[19] Numerous studies have reported high use of NSAIDs among MC patients. In a retrospective review of 163 patients in Sweden with CC, 34% were taking NSAIDs on a regular or sporadic basis.[35] Another Scandinavian study showed that 35% of the 104 patients with MC examined used NSAIDs.[36] In a case control study by Riddell, 31 patients with CC were compared with 31 controls with irritable bowel syndrome or diverticulosis. Long-term use of NSAIDs (for $>6$ mo) was reported in 19 of 31 subjects with MC, compared with only 4 of 31 controls. The case for an etiological role for NSAID use and MC was strengthened by reports of clinical and histologic improvement among NSAID users when the medication was discontinued.[20,23–25] In the controlled study of 31 patients with CC described previously, 3 subjects reported reduction in diarrhea after they stopped taking NSAIDs. One subject, who later resumed taking an NSAID, developed recurrent diarrhea that resolved when the NSAID was again discontinued.[20]

Given this apparent role for NSAIDs in MC, we performed a meta-analyses based on the 3 case-control studies published to date [pooled OR 3.25 (1.1-9.5), see Fig. 2 for forest plot]. Although we did calculate the pooled OR for NSAID exposure, it is important to note that this should be interpreted with caution for the following reasons. First, the number of published studies available for analysis is limited. Second, no correction was possible for other confounders, since Riddell et al[20] did not present adjusted analyses, whereas we had to pool the drug exposure rates of LC and CC for the study by Fernandez-Banares et al[19]before meta-analyses. Third, the studies report on different patients populations (MC pooled together or LC and CC separately) as well as control population (general population, patients controls or a mixture of both). We therefore consider the findings of these meta-analyses indicative rather than conclusive regarding a possible etiological role for NSAIDs.

A potential confounding factor is the presence of coexisting arthralgia in patients with MC, which could increase their use of NSAIDs.[37] A study reported that 18 of 31 (56%) patients with CC had some form of arthritis; and 71% of those were using NSAIDs regularly at the time of diagnosis.[9] Establishment of a cause-effect relationship here is exceptionally challenging and cannot be performed on the basis of the currently available datasets. Nevertheless, several hypotheses can be postulated with regard to potential pathophysiological mechanisms. Intestinal side effects of NSAID have been documented extensively. NSAIDs induce small intestinal and colonic injury and inflammation and possibly may exacerbate IBD.[32] Furthermore, 60% to 70% of patients on long-term NSAID may have asymptomatic enteropathy.[32] NSAID intake has

**TABLE 2.** Case Reports for Nonsteroidal Anti-inflammatory Drug-associated Microscopic Colitis

| Study | Drug | LC or CC | Age | Sex | Other Drugs | Comorbidities | Time Interval Between Start of Drug Use and Onset of Diarrhea | Dechallenge | Time to Cessation of Diarrhea | Histo logic normaliza-tion | Re challenge | Time to Recurrence of Diarrhea | Time to Cessation of Diarrhea | No Recurrence of Diarrhea > 18 mo | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Milman et al[22] | Diclofenac | LC | 41 | F | Etanercept | Psoriatic arthritis | 3 d | + | ND | ND | + | 2d | – | ND | Budesonide |
| Giardiello et al[23] | | | | | | | | | | | | | | | |
| Case 1 | Indomethacine | CC | 60 | M | Enalapril, metozalone | Arthritis | ND | – | ND | ND | ND | ND | ND | ND | Prednisolone Sulfasalazine |
| Case 2 | Indomethacine | CC | 77 | M | ND | *Clostridium difficile* | 2 mo | ND | ND | ND | ND | ND | ND | – | Prednisolone |
| Yagi et al[24] | Aspirin Ticlopidine | CC* | 77 | F | ND | CVA | ND | + | ND | + | ND | ND | ND | ND | — |
| Al-Ghamdi et al[25] | Diclofenac Ketoprofen | CC | 80 | F | Atidronate | Osteoporosis | 6 wk | + | ND | ND | + † | 4 wk | ND | ND | — |

*Endoscopic lesions.
†Rechallenge with ketoprofen, acetylsalicylic acid, and ranitidine.
CC indicates collagenous colitis; LC, lymphocytic colitis, ND, not defined; + , performed; __, none or not performed.

**TABLE 3.** Case Reports Venotonic Medication-associated Microscopic Colitis

| Study | Drug | LC or CC | Age | Sex | Other Drugs | Comorbidities | Time Interval Between Start of Drug Use and Onset of Diarrhea | Dechallenge | Time to Cessation of Diarrhea | Histologic Normalization | Re-challenge | Time to Recurrence of Diarrhea | Time to Cessation of Diarrhea | No Recurrence of Diarrhea > 18 mo | Treat-ment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dharancy et al[26] | Cyclo 3 forte | LC | 37 | F | – | Atopia | 4 wk | + | 3 d | ND | ND | ND | ND | ND | — |
| Beaugerie et al[27] | | | | | | | | | | | | | | | |
| Case 1 | Cyclo 3 forte | LC | ND | F | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | — |
| Case 2 | Cyclo 3 forte | LC | ND | F | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | — |
| Case 3 | Cyclo 3 forte | LC | ND | F | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | — |
| Macaigne et al[28] | Esberivan forte | LC | 84 | M | Alprazolam, venlofaxine | Mitral valve insufficiency depression gastric ulcer | 2 mo | + | ND | + | ND | ND | ND | + | — |

LC indicates lymphocytic colitis, ND, not defined; + , performed; __, none or not performed.

**TABLE 4.** Cohort Studies Assessing Medication Use in Microscopic Colitis

| | Study | | | |
|---|---|---|---|---|
| | **Sveinsson et al[33]** | **Pardi et al[34]** | **Goff et al[31]** | **Bohr et al[35]** |
| Study design | Nation-wide cohort new diagnosed MC patients | Single-center Mayo Clinic | Single-center University Michigan | Registry 25 Swedish hospitals |
| Inclusion period | 1995-1999 | 1997-1999 | Before 1992 | 1989-1995 |
| MC | 125 | 189 | 31 | 163 |
| LC | 71 | 176 | — | — |
| CC | 54 | 6 | 31 | 163 |
| Method | Patient questionnaire | Retrospective chart review | Retrospective chart review and telephone interview | Retrospective chart review |
| NSAIDs at diagnosis | | | | |
| MC | 33% | Aspirin 43.9%<br>Other NSAIDs 24.3%<br>Ticlopidine 3.7%* | — | — |
| LC | 17% | — | — | — |
| CC | 41% | — | 71% | 33.6% |
| Other medication at diagnosis | | Lansoprazole 3<br>Bupropion 2<br>Sertraline 2<br>Colchicine 2<br>Etanercept 1<br>Carvedilol 1<br>Metformin 1<br>Omeprazole 1<br>Valproci acid 1<br>Amitryptyline 1<br>Troglitazone 1<br>Niacin 1<br>Hydrochloroquine 1<br>Cisapride 1 | | |

*For 2 patients on ticlopidine dechallenge resulted in cessation of diarrhea.
CC indicates collagenous colitis; LC, lymphocytic colitis.

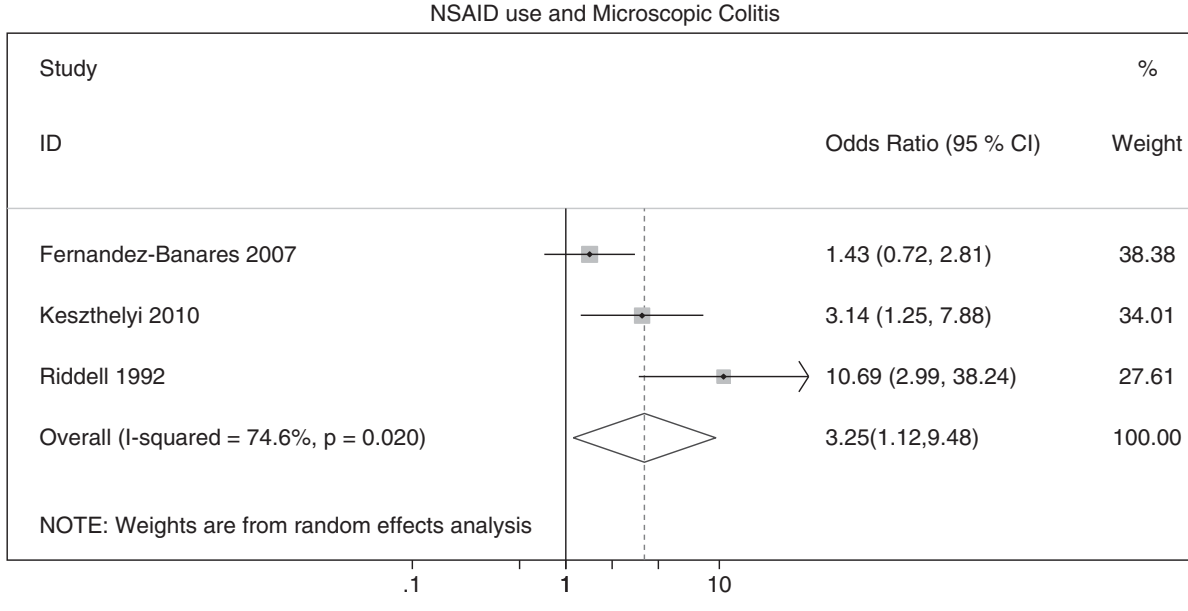


**FIGURE 2.** Forest plots for meta-analysis of nonsteroidal anti-inflammatory drug (NSAID) use in microscopic colitis. CI indicates confidence interval.

in fact been associated with increased risk for acute diarrhea.[38] More recently, Gleeson and Davis[39] reported that 74% of new cases presenting with colitis had been using NSAIDs before the development of their disease.

Therefore, the alleged ability of NSAIDs to cause or at least exacerbate MC is not altogether unexpected. NSAID-related erosions and ulcers are most commonly seen in the distal ileum and rectum. Small intestinal injury due to NSAIDs differs pathophysiologically from that found in the stomach, as prostaglandin suppression does not play an important role.[40] Rather, NSAIDs and bile have synergistic effects with respect to injury of the small intestine by contact irritation of the mucosa. The enterohepatic circulation seems to be crucial in this regard, by allowing repeated exposure to the offending chemicals. In the small intestine, NSAIDs uncouple mitochondrial oxidative phosphorylation leading to reduced intracellular ATP levels. This, in turn, leads to loss of cytoskeletal control over tight junctions and increased paracellular permeability.[41] This increased permeability may allow passage of certain, yet to be identified luminal antigens, which can elicit a malicious immune response, which, provided such mechanism is also present in the colon, may potentially result in clinically manifest MC.

## PPIs

Recent studies have emphasized the association between exposure to PPIs and occurrence of MC. Many case reports have been published that further highlight the association between PPI use and development of MC[42–45] (Table 5). Initially, lansoprazole has been associated with a high likelihood of inducing MC.[50] In most published cases, symptoms started within few weeks after start of lansoprazole therapy (median 21.5 d), and complete resolution after lansoprazole discontinuation was observed within a few days (median 7 d), without need for further therapy.[51] Another recent study also pointed to similar effects in case of exposure to omeprazole and esomeprazole.[45] PPIs are one of the most frequently prescribed classes of medications worldwide because they combine a high level of efficacy with low toxicity. In 2006, expenditure on these drugs was 10 billion USD globally.[52] In the 5 years since the introduction of esomeprazole in 2001, prescriptions for PPIs have doubled.[52] It is noteworthy, that the increasing incidence of MC[4] seems to parallel the rising use of PPIs.

Besides a number of case reports and case series, only a very limited number of controlled studies have examined the role of PPI exposure in MC,[18,19] of which only one found a positive association.[18] More comprehensive studies are still lacking for PPIs to support an etiological role for PPIs in MC.

The potential pathophysiological mechanisms underlying PPI-related induction of MC are poorly understood. When patients are prescribed PPIs to treat upper gastrointestinal disorders, it is important to recognize that PPIs are interacting at multiple targets. Proton pumps ($H^+/K^+$ ATPases) are present not only on gastric epithelium but also on colonic epithelium where they contribute to whole-body potassium homeostasis.[53] Inhibition of the colonic proton pumps may therefore affect local electrolyte balance and compromise fluid acidification, which can possibly affect immune reactions in the colonic mucosa. Autoradiographic studies using $^3$H-lansoprazole in animal models have shown uptake of the drug in the colonic mucosa, both in upper colonic epithelial cells as well as in inflammatory cells.[54]

Proteins other than $H^+/K^+$ ATPase have also been reported as targets for PPIs. Omeprazole and lansoprazole have been observed to induce smooth muscle relaxation and to inhibit contractile activity.[53] This effect on contractile systems may also affect tight junction functionality as tight junction proteins are directly linked to the actinomyosin cytoskeleton. Therefore, conformational changes in the cytoskeleton of epithelial cells may result in alterations in the function of the tight junction, which leads to increased paracellular permeability. As a result, luminal contents can more easily penetrate the lamina propria causing an immune and/or inflammatory reaction. Esomeprazole has been shown to increase paracellular permeability in the upper gastrointestinal tract in vitro[55] and in vivo in humans.[56] Increased paracellular permeability has been observed in MC and is considered a key component in the induction of diarrhea.[57] Accordingly, expression of the tight junction proteins occludin, claudin-4, and zonula occludens-1 was found to be decreased in mucosal biopsy specimens from MC patients.[57,58] We speculate that a direct or indirect effect of PPIs on colonic tight junctions and paracellular permeability, similar to that of NSAIDs, may be a potential mechanism in the development of MC.

Recent case reports have related the occurrence of severe hypomagnesemia to long-time PPI exposure.[59,60] This effect has been described for omeprazole, esomeprazole, pantoprazole, and lansoprazole.[59] It has been proposed that PPIs induce a defect in the active absorption of magnesium in the intestine. This may result from an effect of PPIs on the tight junction proteins or on the TRPM6 and 7 channels (transient receptor potential melastin 6 and 7). The latter are key molecules involved in active magnesium absorption. Either changes in intestinal pH induced by PPIs may affect channel functions, or subjects who are heterozygous carriers of TRPM6/7 mutations are more susceptible to developing adverse reactions to PPIs.[60] Presently, we cannot exclude that effects of PPIs on magnesium absorption have a role in the pathogenesis of MC. The fact that distinct genetic profiles can be of superior importance with regard to the development of side effects during PPI therapy is further supported by reports describing agranulocytosis and neutropenia induced by PPI.[61] A recent report demonstrated that this is caused by a mutation of the CYP2C19*17, the enzyme responsible for PPI metabolism.[62]

In addition, it is well known that PPI therapy affects intestinal microbial profiles.[63–66] Several bacteria, including *Helicobacter pylori* and *Streptococcus pneumoniae*, as well as fungi such as *Candida albicans*, contain $H^+/K^+$ ATPase in their plasma membranes that are highly homologous to their human counterparts.[67] PPIs can therefore directly influence microbial growth by inhibition of the $H^+/K^+$ ATPase. In contrast, increase of intestinal pH can result in a diminished host defense against certain bacteria. Profound acid suppression increases the risk of enteric infections in susceptible individuals caused by *Shigella*, *Salmonella*, *Yersinia*, or *Clostridium difficile*.[68] The use of PPIs may also promote the expansion and colonization of *C. difficile* by its recognized potential to induce small bowel bacterial overgrowth with anaerobic colonic organisms.[63] Many clinicians believe that PPI use may therefore directly contribute to *C. difficile* and other bacterial infections. The FDA has in fact recently issued a

**TABLE 5.** Case Reports of Microscopic Colitis Associated With Proton Pump Inhibitors

| Study | Drug | LC or CC | Age | Sex | Other Drugs | Comorbidities | Time Interval Between Start of Drug Use and Onset of Diarrhea | De-challenge | Time to Cessation of Diarrhea | Histologic Normalization | Re-challenge | Time to Recurrence of Diarrhea | Time to Cessation of Diarrhea | No Recurrence of Diarrhea > 18 mo | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ghilain et al[46] | | | | | | | | | | | | | | | |
| Case 1 | Lansoprazole | LC | 60 | M | — | Adenoma | 6 wk | + | xd | + | ND | ND | ND | 3 mo | — |
| Case 2 | Lansoprazole* | LC | 55 | M | Alodipine<br>Cavedilol | Angina pectoris<br>Hypertension | 8 wk | + | 2 d | + | ND | ND | ND | ND | — |
| Chande and Driman[42] | | | | | | | | | | | | | | | |
| Case 1 | Lansoprazole* | CC | 78 | F | ND | Constipation | 6 wk | + | 2 wk | + | ND | ND | ND | ND | — |
| Case 2 | Lansoprazole | CC | 65 | F | ND | Gastritis | 2 wk | + | 4 wk | + | ND | ND | ND | ND | — |
| Mukherjee[47] | Lansoprazole | MC† | 40 | M | — | GERD | 4 wk | + | 3 d | ND | ND | ND | ND | ND | Sulfasalazine |
| Wilcox and Mattia[45,48] | | | | | | | | | | | | | | | |
| Case 1 | Lansoprazole | CC | 51 | F | Estradiol | GERD | xd | + | ND | + | + | 1 wk | ND | ND | — |
| Case 2 | Omeprazole<br>Esomeprazole | LC | 82 | M | Coumadin<br>Digoxin<br>Furosemide<br>Paroxetin<br>Simvastatin | Atrial fibrillation<br>Duodenal ulcer | 20 mo | + | 2 wk | ND | ND | ND | ND | ND | — |
| Case 3 | Omeprazole* | LC | 59 | M | Atorvastatin<br>Metformin<br>Metoprolol<br>Hydrochlorthiazide<br>Indomethacin | GERD<br>Diabetes mellitus type 2 | 5 y | + | ND | + | ND | ND | ND | + | — |
| Case 4 | Esomeprazole* | MC | 84 | M | Coumadin<br>Prednisone<br>Furosemide<br>Metoprolol | Polymyalgiarheumatica<br>Atrial fibrillation<br>Diverticulosis | 4 y | + | 4 d | + | + | 1 wk | 2 d | + | — |
| Case 5 | Omeprazole* | LC | 65 | F | — | GERD<br>Diverticulosis | 1 y | + | ND | ND | + | 2 mo | ND | + | — |
| Thomson et al[44] | | | | | | | | | | | | | | | |
| Case 1 | Lansoprazole‡ | LC | 77 | M | Librax<br>Donnatal lisinopri<br>Hydrochlorthiazide<br>Metoprolol | GERD<br>Hypertension<br>Asbestosis | 1 mo | + | xd | + | ND | ND | ND | ND | — |
| Case2 | Lansoprazole‡ | LC | 76 | M | Metoprolol<br>Amlodipine<br>Isordil<br>Glyburide | Diabetes mellitus type 2<br>Coronary artery syndrome<br>GERD<br>Depression | ND | + | xd | + | ND | ND | ND | ND | — |
| Case3 | Lansoprazole‡ | LC | 69 | M | Prazosin<br>Gemfibrosil<br>Acetaminophen | Barrett alcoholism<br>Prostate cancer<br>COPD | 5 d | + | 10 d | + | ND | ND | ND | ND | — |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case4 | Lansoprazole | LC | 54 | M | Simvastatin<br>Sertralin<br>Folate<br>Acetaminophen | Coronary artery syndrome<br>Hypercholesterolemia<br>Depression<br>Low back pain GERD | xd | + | 4 d | + | ND | ND | ND | ND | — |
| Case5 | Lansoprazole‡ | CC | 51 | M | Metamucil<br>Nifedipine<br>Desipramin | Depression<br>Hypertension<br>IBD<br>Diverticulitis | 1 wk | + | xd | + | ND | ND | ND | ND | — |
| Case 6 | Lansoprazole‡ | MC | 75 | M | Warfarin<br>Metoprolol<br>Furosemide<br>Captopril<br>Oxazepam<br>Propoxyphene | Atrial fibrillation<br>Coronary artery syndrome<br>Osteoarthritis<br>Nephrolithiasis<br>GERD | 4 mo | + | 5d | + | ND | ND | ND | ND | — |
| Rammer et al[49] | Lansoprazole | CC | 57 | M | ND | ND | 4 wk | + | ND | + | ND | ND | ND | ND | — |
| Hilmer et al[43] | | | | | | | | | | | | | | | |
| Case 1 | Lansoprazole | LC | 78 | F | Aldronate<br>Hydrochlorthiazide<br>Irbesartan<br>Aspirin<br>Thiamine<br>Vitamin C<br>Glucosamine | — | 2 mo | + | 2 d | ND | ND | ND | ND | ND | — |
| Case 2 | Lansoprazole | LC | 53 | F | Gemfibrozil<br>Tibone<br>Indapamine<br>Perindopril | GERD | 9 mo | + | 6 mo | ND | ND | ND | ND | ND | Budesomide<br>Cholestyramine |
| Case 3 | Lamsoprazole§ | LC | 79 | F | Alendronate<br>Perindopril<br>Chlortalidone<br>Potassium Chloride<br>Celecoxib | ND | 2 wk | + | 1 mo | ND | ND | ND | ND | ND | — |

*No diarrhea with rabeprazole.
†Only 5% intrepihelial lymphocytes, no recurrence of diarrhea with omeprazole.
‡No symptoms with omeprazole before or after lansoprazole.
§Patient also took celecoxib. Dechallenge of lansoprazole and celecoxib.
CC indicates collagenous colitis; LC, lymphocytic colitis; ND, not defined; xd, few days; +, performed; __, none or not performed.

safety announcement that PPI use may be associated with *C. difficile* infection.[69] A recent study by Lombardo et al[70] also suggested that PPI therapy in humans may potentially result in small intestinal bacterial overgrowth. Whether these changes in intestinal microbiota induced by PPI therapy are truly responsible for the development of symptoms and clinical conditions remains subject to considerable discussion.[71] Further research is needed to clarify the exact effects of PPIs on human intestinal microbiota.

Nevertheless, alterations in intestinal microbiota should also be considered as a possible pathogenetic factor in MC. The role of microbiota in regulating intestinal function has increasingly been appreciated and perturbation of intestinal microbiota seems plausible in MC.[72] The anatomic sites of highest bacterial concentration in the gut (cecal and right colon) are the sites most frequently affected by inflammation.[30] There is also some, albeit not robust, evidence that CC patients may benefit from treatment with probiotics.[73]

### Coexposure to NSAIDs and PPIs

PPIs and NSAIDs are often used simultaneously, with the former frequently coprescribed to reduce gastrointestinal injury due to the latter. Recent video capsule studies suggest[74,75] a very high incidence (55% to 70%) of intestinal damage in healthy humans taking both NSAIDs and PPIs for 2 weeks. A more recent study performed in rats demonstrates that PPIs induced a marked exacerbation of small intestinal ulceration induced by NSAIDs, which was transferable to germ-free mice through microbiota isolated from the PPI-treated rats, suggesting an important role for microbial alterations. When PPIs were administered alone, significant changes in intestinal microbiota were observed, with 80% reduction in the levels of the beneficial *Bifidobacteria* spp., whereas little morphological effect was detected on the intestinal mucosa.[76]

Overall, it is tempting to assume that PPIs can potentially induce alterations in intestinal microbiota, albeit not to a clinically significant degree, which can in turn impair the capacity of the intestine to respond to potentially noxious agents, such as NSAIDs, known also to affect intestinal barrier function. Such a "2-hit" theory could provide an explanation for the relevance of coexposure to PPIs and NSAIDs in the development of MC. Recent results suggest a higher intake of PPIs with NSAIDs in patients with MC compared with controls from the general population.[18] However, in the published case reports, only 2 of 20 patients were using PPIs and NSAIDs simultaneously. Further studies are warranted to provide confirmative evidence on this potential additive effect of coingestion.

### Other Drugs

A number of other drugs have been proposed to be associated with MC (Table 6). Ticlopidine, for instance, has also been reported in a number of cases to be the cause of MC. The possible underlying mechanism was suggested to be related to induction of apoptosis of epithelial cells in the colonic crypts.[83] Other drugs that have been associated with the induction of MC include ranitidine,[79] acarbose,[84] the venotonic drug Cyclo 3 forte, flutamide,[30] β-blockers,[19] and statins.[85] The association of statins with colitis has been based on an ischemic pathophysiology.[86]

## CONCLUSIONS

Diarrhea is a frequent adverse event induced by drugs, accounting for about 7% of all adverse effects of drug therapy and over 700 drugs have been claimed to cause diarrhea.[87] Drugs or their metabolites may cause diarrhea directly through their pharmacological properties or through idiosyncratic hypersensitivity reactions. Furthermore, drugs can alter the colonic microbiota and subsequently cause diarrhea.

The concept that some drugs may cause or worsen MC was first proposed in the 1990s.[20,23] Olesen et al[88] estimated 10% of all MC cases to be induced by drugs. The low frequency of MC associated with drugs of different pharmacodynamic profile, on the other hand, favors the pathophysiological mechanism to be of idiosyncratic nature. Resolution of symptoms after discontinuation of a drug and recurrence of diarrhea after rechallenge is a strong argument for such an idiosyncratic drug reaction. In a recent literature review, Beaugerie and Pardi[50] suggested the use of a scoring system to determine the strength of evidence that associated individual drugs or drug classes with MC. NSAIDs, aspirin, PPIs, ranitidine, selective serotonin reuptake inhibitors, ticlopidine, acarbose, and statins had high or intermediate levels of association with the disease. Carbamazepine, flutamide, and paroxetine had less well-established associations with MC. A more recent study indeed confirmed a role for NSAIDs, selective serotonin reuptake inhibitors, statins, and PPIs, but also bisphosphonates and β-blockers.[19] Reports have also proposed that aspirin, sertraline, simvastatin, and lanzoprazole may be more likely to be associated with MC than other medications in the corresponding classes.[19,50]

In principle, the causative role of a certain drug can be proven by demonstrating that (a) intake of the drug precedes the manifestation of disease, (b) discontinuation of a certain drug results in symptom resolution (dechallenge), (c) recurrence of the disease when medication is resumed (rechallenge), and (d) other causes of disease have been excluded. However, for most drugs having been associated with MC, rechallenge has not been performed or reported and the number of cases is small, such that an association by chance cannot be ruled out. Apart from case reports, the very limited number of retrospective studies assessing medication use and presence of disease generally do not allow to establish a cause-effect relationship as such studies are largely confounded by other factors, such as comorbid conditions, for which the use of certain pharmacological therapy is indicated. Furthermore, depending on the methods used for data acquisition, recall bias can largely influence drug exposure rates. Performing such studies aimed at defining certain associations in MC is challenging considering the higher age of patients affected and thereby frequent medication use. Such approaches should, however, be able to shed light on a positive association between the use of certain drugs and the disease condition. This enables the formulation of working hypotheses, provided that biological plausibility to ascertain a legitimate causative role of a drug is present.

Several factors can be found to explain a positive association with drug exposure and MC, apart from a cause-and-effect relationship. First, as for NSAIDs, many drugs that are associated with MC, including PPIs, induce watery diarrhea as common adverse effect. Thus, by causing or worsening diarrhea, use of these drugs can result in identification of MC, rather than being the primary etiological factor.

**TABLE 6.** Case Reports of Microscopic Colitis Associated With Other Drugs

| Study | Drug | LC or CC | Age | Sex | Other Drugs | Comorbidities | Time Interval Between Start of Drug Use and Onset of Diarrhea | De-challenge | Time to Cessation of Diarrhea | Histo-logic Normali-zation | Re-challenge | Time to Recurrence of Diarrhea | Time to Cessation of Diarrhea | No Recurrence of Diarrhea > 18 mo | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Maroy[77] | | | | | | | | | | | | | | | |
| Case 1 | Entacapone | LC | 76 | F | Levodopa-carbidopa Enlafaxine | Morbus parkinson | 14 wk | + | ND | + | +* | – | ND | + | — |
| Case2 | Entacapone | LC | 81 | M | Pirebidil Levodopa-carbidopa | Morbus parkinson | 3 wk | + | 10 d | + | ND | ND | ND | + | — |
| Case 3 | Entacapone | LC | 75 | M | Levodopa-carbidopa | Morbus parkinson | 10 wk | + | 2d | ND | + | 2 d | 2 d | + | — |
| Chauveau et al[78] | Vinburnine | LC | 62 | M | ND | ND | 15d | + | 2 wk | + | ND | ND | ND | ND | — |
| Beaugerie et al[79] | Ranitidine | LC | 69 | F | Levothyroxin Paracetamol | Toxic goiter, psoriatic arthritis | 10d | + | 2 d | – | + | 2 d | ND | ND | ND |
| Hawe and Bolton[80] | Clozapine | MC | 62 | F | — | — | 16 d | + | 8 d | ND | + | 8 d | 10 d | ND | — |
| Bechade et al[81] | Mianserine | LC | 65 | F | Moclobemide | Depression Right hemicolectomy Adenoma | 2 d | +† | 3 wk | + | ND | ND | ND | ND | Budesonide Cholestyramine |
| Macaigne et al[82] | Piascledine | LC | 40 | F | Paroxetine | Depression | 6 wk | + | 8 d | + | ND | ND | ND | 6 mo | — |

*Rechallenge reduced dose 200 mg.
†Dechallenge and start budesonide and cholestyramine.
CC indicates collagenous colitis; LC, lymphocytic colitis, ND, not defined; +, performed; __, none or not performed.

Second, one should consider that greater awareness of physicians and subsequent increase in exposure to colonoscopy with biopsy among patients receiving these medications may merely lead to an apparent increase in the diagnosis of MC.

Third, the growing list of distinct drugs and drug classes potentially associated with MC, and largely variable time interval between start of drug use and onset of MC symptoms, indicate the great difficulty in establishing an association between specific agents and MC.[35] Nevertheless, because of the associations between MC and NSAIDs, PPIs, and other medications, in individual cases, drug use and recent history should be carefully reviewed in patients with watery diarrhea or newly diagnosed MC. Agents that cause symptoms might be identified based on the temporal relationship between the timing of drug use and onset of symptoms.

The fact that most case reports of drug-induced MC concern *suspected* adverse drug reactions remains an inherent problem in pharmacovigilance. Adverse reactions are rarely specific for the drug and a rechallenge, which can add suggestive evidence for a causative role, is rarely ethically justified. In an attempt to solve this problem, many systems have been developed for a structured and harmonized assessment of causality, the most commonly used being the WHO-Uppsala Monitoring Center[89] and the Naranjo criteria.[90] None of these systems, however, have been shown to produce a precise and reliable quantitative estimation of relationship likelihood resulting in a lack of international consensus regarding causality assessment.

Nevertheless, valid arguments for causality have been provided by studies showing marked improvement in symptoms or histology after stopping the drug and in some cases rechallenge resulting in symptom relapse. Overall, evidence exists to support the role of certain drugs, in particular NSAIDs and PPIs, are able to contribute to the development of MC. In terms of disease development, it is tempting to assume that MC induced by a heterogeneous group of drugs possibly shares a common multistep pathophysiology related to the impairment of the intestinal epithelial barrier. Drug-induced impairment of the barrier may set the stage for further, as yet undetermined, insults through a luminal antigen that precipitates the disease. By virtue of interfering with intestinal homeostasis, they may potentially initiate or exacerbate ongoing unfavorable mucosal immune activation resulting in clinically manifest MC. Even though accumulating evidence suggests a role for certain drugs in disease development, it is obviously not the sole factor in MC.

In conclusion, we systematically reviewed the literature on medication use and MC. In individual cases, drugs such as NSAIDs and PPIs should be considered as potential etiological factors. Patients taking these drugs may therefore warrant investigation for MC when developing watery diarrhea. It is crucial to ascertain the temporal relationship between exposure and symptom onset to support a causative role. After diagnosis, attempt should be made to discontinue the suspected drug. Although a number of hypotheses have been formulated with regard to potential pathophysiological mechanisms in drug-induced MC, confirmative evidence is still largely lacking. Given the wide use of these drugs among the general population and the relative rarity of the condition, drug-induced MC seems to be an uncommon complication, which most probably simply reflects an unfortunate idiosyncratic reaction to the particular drug.

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